



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

006239

AUG 27 1987

Memorandum

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Subject: Inert Chemical: CGA-154281, 4-(dichloroacetyl)-3,4-dihydro-3-methyl-2H-1,4-benzoxazine, EPA Identification No. 7E3489 - Used as An Inert Ingredient in Pesticide Formulations containing Metolachlor. Caswell No. 298C

From: John H.S. Chen, D.V.M.
Review Section I
Toxicology Branch
Hazard Evaluation Division (TS-769C)

John H.S. Chen 8/21/87

To: Kerry Leifer, PM 45
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Registration Division (TS-767C)

Thru: Robert B. Jaeger, Section Head
Review Section I
Toxicology Branch
Hazard Evaluation Division (TS-769C)

*8/21/87
for WBS
8/27/85*

Action Requested:

1. Review and assessment of the toxicological studies with CGA-154281 Technical.
2. Request for exemption from the requirement of tolerance for residues of CGA-154281 Technical under 40 CFR 180.1001(d).

Petitioner:

CIBA-GEIGY Corp. Agricultural Division, Greensboro, NC 27419

Recommendation:

1. The registrant should be apprised of the deficiencies noted in the following studies which are identified in the detailed review:

A. Acute Inhalation Toxicity Study in Rats. CIBA-GEIGY Corp. Division of Toxicology/Pathology Project No. 86042, July 28, 1986. Supplementary.

B. Rabbit Teratology Study with CGA-154281. HLA Project No, 483-246. October 10, 1986. Supplementary.

C. Micronucleus Test (Chinese Hamster). CIBA-GEIGY Corp. Experimental Pathology Laboratories Report No. 860109. November 3, 1986. Unacceptable.

D. Autoradiographic DNA Repair Test on Human Fibroblasts. CIBA-GEIGY Corp. Experimental Pathology Laboratories Report No. 860178. August 25, 1986. Unacceptable.

2. The following toxicological studies support the data requirements for inert ingredients identified in the inert strategy document (Federal Registra/Vol. 52, No.77, April 22, 1987. Pg. 13308):

A. Subchronic Toxicity Study in Rats. HLA Project No. 483-247. September 26, 1986. NOEL = 100 ppm; LEL = 300 ppm (kidney nephrosis). Core Minimum.

B. Subchronic Toxicity Study in Dogs (1) HLA Project No. 483-244. August 14, 1986 and 90-day Oral Toxicity Study in Dogs (2) HLA Project No. 483-247. September 30, 1986. NOEL = 5 mg/kg/day; LEL = 50 mg/kg/day (increased liver/gallbladder weight). Core Guideline.

C. 21-day Dermal Toxicity in Rabbits. CIBA-GEIGY Corp. Division of Toxicology/Pathology Project No. 86068. October 9, 1986. No irritation at 5 mg/kg/day. Core Guideline.

D. Rat Teratology Study with CGA-154281. HLA Project No. 483-245. August 20, 1986. Maternal Toxicity NOEL = 100 mg/kg/day; Developmental Toxicity NOEL = 100 mg/kg/day. Core Minimum.

E. Salmonella/Mammalian-Microsome Mutagenicity Test. CIBA-GEIGY Corp. Experimental Pathology Laboratories Project No. 860840. September 15, 1986. Positive response at 2000-8000 ug/plate W/O S9; Positive response at 4000-5000 ug/plate W/S9. Acceptable.

F. Salmonella/Mammalian-Microsome Mutagenicity Test. CIBA-Geigy Corp. Experimental Pathology Laboratories Project No. 86076. October 17, 1986. Positive response at 1000 ug/plate W/S9 and W/O S9. Acceptable.

G. Autoradiographic DNA Repair Test on Rat Hepatocytes. CIBA-GEIGY Corp. Experimental Pathology Laboratories Project No. 860177. October 24, 1986. Positively causing DNA damage inducible repair. Acceptable.

In addition, the following toxicological studies have been reviewed and are acceptable as described:

A. Primary Dermal Irritation in Rabbits. CIBA-GEIGY Corp. Division of Toxicology/Pathology Project No. 86050. May 21, 1986. No irritation; Toxicity Category IV.

B. Guinea Pig Skin Sensitization Study. Stillmeadow, Inc. Biological Testing Laboratory Project No. 4001-86. March 28, 1986. Sensitizing agent at 500 mg. Core Guideline.

C. Acute Oral Toxicity in Rats. CIBA-GEIGY Corp. Division of Toxicology/Pathology Project No. 86044. May 20, 1986. LD50 > 5000 mg/kg (both sexes); Toxicity Category IV.

D. Acute Dermal Toxicity in Rabbits. CIBA-GEIGY Corp. Division of Toxicology/Pathology Project No. 86026. May 21, 1986. LD50 > 2010 mg/kg (both sexes); Toxicity Category III.

E. Primary Ocular Irritation in Rabbits. CIBA-GEIGY Corp. Division of Toxicology/Pathology Project No. 86052. July 30, 1986. Moderate ocular irritation; Toxicity Category II.

F. Metabolism of CGA-154281 in the Rat. CIBA-GEIGY Corp. Biochemistry Department Project No. ABR-86079, RPT-49-554, and ABR-86081. November 18, 1986. The major route of excretion were via elimination in the urine (73-82%) and feces (11-21 %). Total residues in tissues were less than 0.5% of the administered dose. CGA-154281 was rapidly metabolized in the rat and the resulting 6 urine metabolites were also rapidly excreted in the urine. Core Guideline.

3. The specific inerts in the confidential statement of formula are cleared under 180.1001 (d). Of the intentionally added inerts, [REDACTED] is exempted. Impurities in formulation are not considered inerts and do not require exemption.

4. Although the Registrant has satisfied the data requirements identified in FR Vol.52, No.77, April 22, 1987, the Agency's HIRG (Hazard Evaluation Inerts Review Group) panel has identified a need for a long term rodent chronic feeding/ oncogenic bioassay. This decision is based on the positive findings in several mutagenicity studies with CGA 154281 and its structural relationship to metolachlor, a class "C" oncogen. Additional input is requested with regard to the nature and quantity of residues likely to occur when used with formulations containing metolachlor.

INERT INGREDIENT INFORMATION IS NOT INCLUDED